

B-LACTAMASE INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to the use of certain β -lactamase inhibitors in conjunction with one or more β -lactam antibiotics for the treatment of *Stenotrophomonas maltophilia*, tuberculosis or *Pseudomonas* species infections.

BACKGROUND OF THE INVENTION

[0002] The effective treatment of many fatal bacterial infections is underpinned by the administration of a course of β -lactam antibiotics. However, increasing resistance to β -lactam antibiotics is reducing the effectiveness of β -lactam antibiotics, thereby necessitating the need for improved antibiotic treatments.

[0003] β -Lactamases are the most commonly encountered cause of resistance to β -lactam antibiotics, which are the most frequently prescribed class of antibacterial drug worldwide [1-3]. β -lactamases render β -lactams inactive through two steps that involve acylation and de-acylation, which ultimately results in hydrolysis of the β -lactam ring [4, 5]. There are hundreds of β -lactamases known, but they can be grouped based on amino acid sequence into the serine β -lactamase (SBL) Classes A, C and D, and the metallo- β -lactamase (MBL) Classes B1, B2 and B3 [6, 7]. Clinically useful β -lactamase inhibitors are being sought, but the varying chemistries and active site architectures of the different classes makes the development of cross-class inhibitors extremely challenging [8-10].

[0004] Clavulanic acid is an example of a β -lactam-based inhibitor principally of class A SBLs that has been used clinically for many years. Most commonly it is used in combination with penicillin derivatives, such as amoxycillin and ticarcillin, to enhance their bactericidal effects against some β -lactamase-carrying isolates of species such as *E. coli* and *K. pneumoniae* [11-14]. Clavulanate (and the related compounds tazobactam and sulbactam) are in effect irreversible inhibitors whose activity arises from fragmentation of the acyl-enzyme complex formed by reaction with the active-site serine nucleophile, to generate inactivated species [15]. In contrast, avibactam is a non- β -lactam-based β -lactamase inhibitor containing a diazobicyclo heterocyclic core structure which acylates SBLs, at least in some cases reversibly, and has a broader spectrum of activity than clavulanic acid. The potency of avibactam against Class A, C and some Class D SBLs is attributed in part to the stabilization of the carbamoyl complex due to formation of a stable acyl-enzyme complex due to interactions with polar residues present in the active site [16-18]. Avibactam has recently been licensed for clinical use in partnership with the oxy-amino cephalosporin ceftazidime, though the combination is not universally efficacious and has no activity against MBL-producing bacteria [17, 19].

[0005] One particular bacterial species that displays widespread resistance to almost all known β -lactams is *Stenotrophomonas maltophilia*. *S. maltophilia* is one of the most intrinsically drug resistant bacterial species to be encountered in the clinic. It causes serious infections with high mortality rates in immunocompromised and severely debilitated patients, and is a colonizer of the lungs of 30% of cystic fibrosis patients [23, 24]. While *S. maltophilia* possesses multiple efflux systems [25-28] that reduce the net

rate of entry for many antimicrobials, β -lactam resistance arises primarily from production of two β -lactamases, a subclass B3 MBL "L1", which hydrolyses all β -lactams except for the monobactam, aztreonam, and the class A Extended Spectrum SBL (ESBL) "L2", which hydrolyses all first to third generation cephalosporins, all penicillins and aztreonam [29-31]. The combination of L1 and L2, therefore renders *S. maltophilia* resistant to all β -lactam antibiotics, although in clinical practice, ceftazidime can be useful because most clinical isolates do not produce enough β -lactamase to cause resistance [32, 33]. However, resistant mutants rapidly emerge through hyper-production of L1 and L2, via single site mutations either in the L1/L2 transcriptional activator, ampR, or in several possible genes whose products influence AmpR [33, 34]. Accordingly, *S. maltophilia* represents one of the most challenging targets for β -lactam/ β -lactamase inhibitor combinations.

[0006] There therefore remains a need for new and effective combination therapeutic products that are effective in the treatment of bacterial infections, such as, for example, *S. maltophilia* bacterial infections.

[0007] The treatment of tuberculosis is also a significant challenge [see, for example, Kasik, J. E., *Am. Rev. Respir. Dis.* 91, 117-119 (1965); Flores, A. R. et al., *Microbiology* 151, 521-532 (2005); Chambers, H. F. et al., *Clin. Infect. Dis.* 26, 874-877 (1998); Donald, P. R. *Scand. J. Infect. Dis.* 33, 466-469 (2001)] along with *Pseudomonas* infections (which can be common in cystic fibrosis patients), so novel therapies to treat these infections are also required.

[0008] The present invention was devised with the foregoing in mind.

SUMMARY OF THE INVENTION

[0009] The present invention relates to the use of the particular cyclic boronate β -lactamase inhibitors defined herein for the treatment of *Stenotrophomonas maltophilia*, tuberculosis or *Pseudomonas* infections (suitably for the treatment of *Stenotrophomonas maltophilia* infections).

[0010] Thus, in one aspect, the present invention provides a β -lactamase inhibitor of Formula I as defined herein, or a pharmaceutically acceptable salt thereof, for use in combination with a β -lactam antibiotic for the treatment of an infection caused by *Stenotrophomonas maltophilia*, tuberculosis and/or *Pseudomonas* species (suitably for the treatment of an infection caused by *Stenotrophomonas maltophilia* species).

[0011] In another aspect, the present invention provides the use of a β -lactamase inhibitor of Formula I, as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of *Stenotrophomonas maltophilia*, tuberculosis and/or *Pseudomonas* infections in combination with a β -lactam antibiotic (suitably for use in the treatment of *Stenotrophomonas maltophilia* infection in combination with a β -lactam antibiotic).

[0012] In another aspect, the present invention provides a method of treating a *Stenotrophomonas maltophilia*, tuberculosis and/or *Pseudomonas* infection, the method comprising administering to a patient in need of such treatment a β -lactamase inhibitor of Formula I as defined herein, or a pharmaceutically acceptable salt thereof, in combination with a β -lactam antibiotic. In an embodiment, present invention provides a method of treating a *Stenotrophomonas maltophilia* infection, the method comprising administering